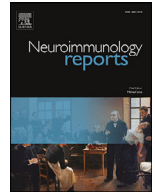




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## Serum negative neuromyelitis optica spectrum disorder after vaxzevria vaccination: A case report

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### ABSTRACT

**Background:** Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease, targeting the central nervous system, rarely associated with vaccination.

**Case report:** We report a case of a 47 year-old healthy woman who presented, ten days after the first dose of SARS-CoV-2 Vaccine AstraZeneca (Vaxzevria), with back pain, tetraplegia, urinary retention, dysarthria and dysphagia. The patient was diagnosed NMOSD. She underwent intravenous-corticosteroids, vein-Immunoglobulin and plasma-exchange without significant improvement.

**Conclusion:** The absence of any possible related conditions, the temporal relation with anti-SARS-CoV-2 vaccination, suggest that, in our case, NMOSD may be due to the cross reaction from Vaxzevria.

### Case report

A 47-year-old right-handed healthy woman with no family history of autoimmune disorders had a 3 days history of back and lower extremity pain with gradual weakness and paresthesias of the legs, accompanied by urinary retention. This progressed to involve all extremities and ultimately an inability to stand. She reported no prior neurological or respiratory or gastrointestinal illness preceding the onset of symptoms. She was receiving no medications. Ten days prior to the onset of symptoms, she received the first dose of Vaxzevria. Examination revealed a severe proximal muscle weakness with a total sensory loss on the trunk, upper and lower extremities with a C3 sensory level. There was diffuse hyporeflexia. Plantar response was silent and no clonus was noted. The day after the patient became dysarthric and disphagic.

Magnetic resonance imaging (MRI) revealed extensive intramedullary STIR and FLAIR hyperintensity extending from the cervical medullary junction throughout the length of the thoracic cord (Figure 1 A) and an abnormal signals on FLAIR and DWI acquisitions in the right middle cerebellar peduncle and left temporal lobe (Figure 1B). Post-gadolinium enhancing was present only in the cerebellar lesion and in a small portion of the thoracic cord (Figure 1C). Laboratory testing revealed negative results for serum angiotensin-converting enzyme, antinuclear antibodies, rheumatoid factor, antiphospholipid,

anti-aquaporin-4 (Anti-AQP4) and anti-myelin oligodendrocyte glycoprotein (Anti-MOG) antibodies. Laboratory tests for HIV, SARS-CoV-2, Lyme disease, Mycoplasma were also negative. Sedimentation rate and vitamin B<sub>12</sub> levels were normal. Cerebrospinal fluid had a protein concentration of 4.04 g/mL, glucose concentration of 35 mg/dL and a white blood cell count of 4350/ $\mu$ L, with 80% neutrophils. No oligoclonal bands were present.

The PCR-multiplex for Herpes Simplex 1-2-6 virus, Epstein-Barr virus, Cytomegalovirus, Streptococcus agalactiae and pneumonia, Parechovirus, Cryptococcus neoformans/gatti, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis and Escherichia coli K1 were negative. An empiric antibiotic regimen (vancomicine 1g/bid, and meropenem 2g/trid) was in anyway started, together with intravenous methylprednisolone (1 g/d for 5 days). Bacterial and fungal culture results were negative, and three days later, vancomicine and meropenem were stopped. Then, intravenous methylprednisolone was slow tapered over the next three weeks, and plasmapheresis treatment was started. Despite these therapies the patient did not significantly improved. A follow up MRI on the day 14, showed a slight improvement of the radiological picture. Because the little effects of the intravenous methylprednisolone and plasmapheresis the patient was treated with vein-Immunoglobulin (0.4 g/kg for five days), without benefit.

**Abbreviations:** Neuromyelitis optica spectrum disorder, NMOSD; Aquaporin-4 autoantibodies, Anti-AQP4; Myelin oligodendrocyte glycoprotein autoantibodies, Anti-MOG.

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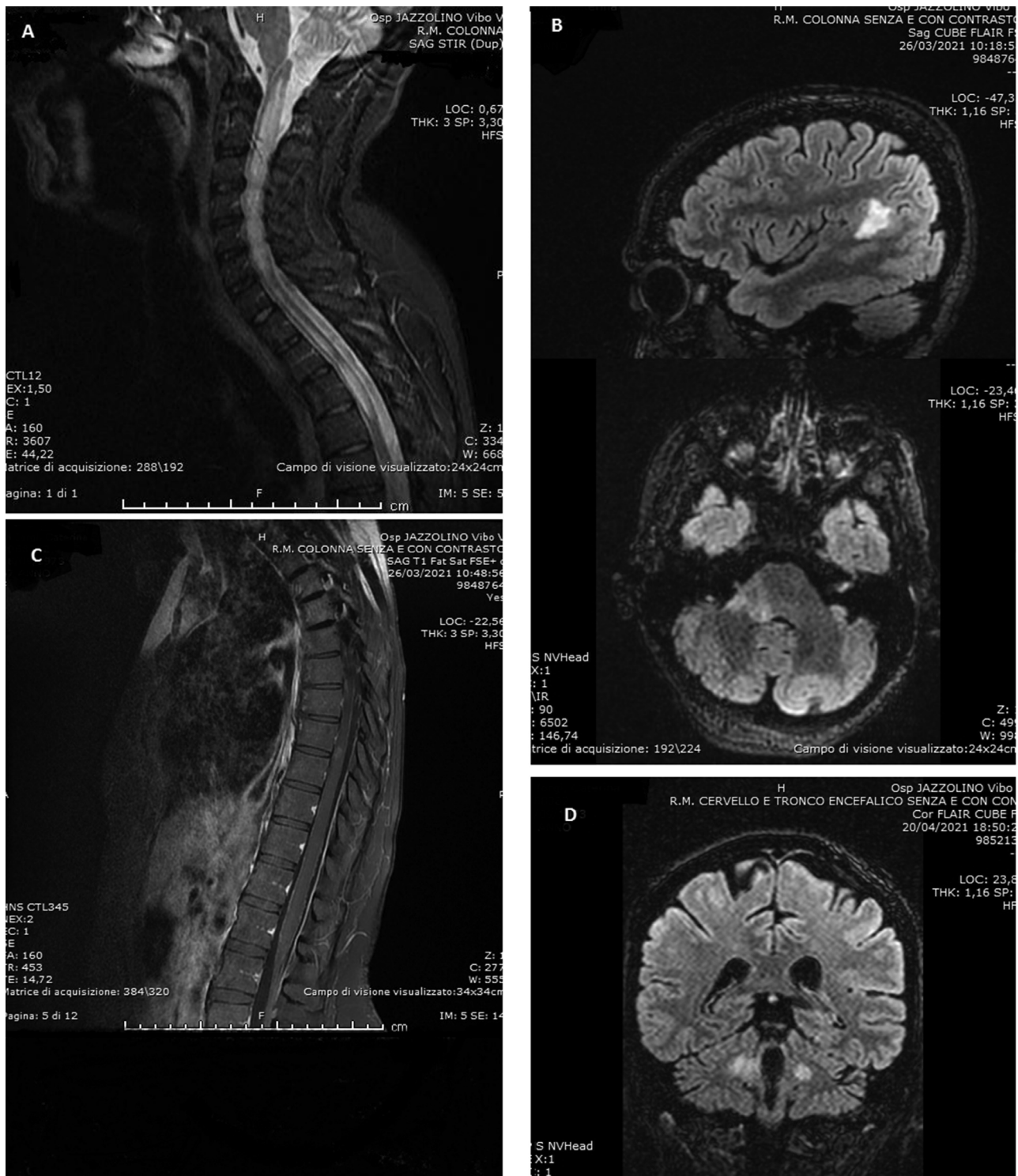
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**Fig. 1.** MRI brain and spine A) STIR hyperintensity extending from the cervical medullary junction throughout the length of the thoracic cord B) FLAIR abnormal signals of the right middle cerebellar peduncle and left temporal lobe. C) Post-gadolinium enhancing of D5-D6 neuromas . D) follow up at day 32 showed a new FLAIR hyperintensity of the left middle cerebellar peduncle.

A second lumbar puncture performed on day 15, showed a protein concentration of 1.37 g/mL glucose concentration of 52 mg/dL and a white blood cell count of 22/ $\mu$ L. On day 32, before the admission to the inpatient rehabilitation facilities, she underwent another MRI, that showed a new hyperintensity of the left middle cerebellar peduncle without post-gadolinium enhancing (Fig. 1 D).

## Discussion

We report findings in a healthy 47-years-old woman who developed a rapid-onset diffuse motor weakness associated with cerebellar dysfunction and cranial nerve abnormalities, ten days after the first dose of Vaxzevira, a recombinant chimpanzee adenoviral vector encoding

**Table 1**

Summary of 2015 international diagnostic criteria for neuromyelitis optica spectrum disorder (modified from [Wingerchuk et al, 2015](#)).

Diagnosis with Anti-AQP4
at least one core clinical characteristic positive Anti-AQP4 with best available method exclusion of alternative diagnosis (eg sarcoidosis, neoplastic/paraneoplastic, vascular, chronic infection).
<b>Diagnosis without Anti-AQP4 /unknown status</b>
at least two core clinical characteristics resulting from one or more clinical attacks and fulfilling the following:
at least one of optic neuritis, longitudinally extensive transverse myelitis, area postrema syndrome
dissemination in space (two or more different core clinical characteristics)
fulfilment of additional MRI requirements as applicable
negative for Anti-AQP4 with best available method, or testing unavailable
exclusion of alternative diagnoses.
<b>Core clinical characteristics</b>
optic neuritis, acute myelitis, area postrema syndrome, brainstem syndrome, symptomatic narcolepsy or acute diencephalic syndrome with NMOSD-typical diencephalic MRI lesions, symptomatic cerebral syndrome with NMOSD-typical brain lesions.
<b>Additional MRI requirements for NMOSD without Anti-AQP4 /unknown status</b>
acute optic neuritis: normal or only non-specific white matter lesions on MRI brain; or optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over $> \frac{1}{2}$ optic nerve length or optic chiasm involvement; acute myelitis: MRI spinal cord demonstrating attack-associated lesion spanning $\geq 3$ contiguous vertebral segments or $\geq 3$ contiguous segments of focal cord atrophy with previous history of acute myelitis area postrema syndrome: dorsal medulla/area postrema lesion on MRI brain: acute brainstem syndrome: periependymal brainstem lesions.

the spike glycoprotein of SARS-CoV-2, approved by regulatory authority for vaccination against SARS-CoV-2 infection. The negative serology results coupled with the negative bacterial and fungal culture results on the cerebrospinal fluid, excluded the possibility of an infectious cause. There was no laboratory evidence of vasculitis or connective tissue disease. The absence of multiple sclerosis-like lesions in the brain, and of oligoclonal bands in the cerebrospinal fluid, and the extensive spinal cord lesion all made multiple sclerosis unlikely. Having effectively eliminated the most probable causes for this patient's condition, we considered, in agreement with the diagnostic criteria of [Wingerchuk et al \(2015; table 1\)](#) the diagnosis of serum negative NMOSD.

NMOSD is a rare autoimmune disease, targeting the central nervous system, mainly characterized by episodes of optic neuritis, myelitis and brainstem syndromes, rarely occurring in the context of other autoimmune diseases (e.g. systemic lupus erythematosus, antiphospholipid antibody, Sjögren's and paraneoplastic syndromes; [Shahmohammadi et al, 2019](#)) or vaccination ([Jarius et al, 2016](#)). Approximately 70% of patients have Anti-AQP4, while Anti-MOG, are present in less than 10% of cases ([Sato et al, 2014](#)). However, the newly revised nomenclature, includes in the NMOSD umbrella, serum-negative patients for Anti-AQP4 and Anti-MOG, in presence of multiple core clinic characteristics and MRI findings ([table one; Wingerchuk et al, 2015](#)).

Our patient presented with acute myelitis and brainstem syndrome; MR showed the presence of an extensive intramedullary hyperintensity and abnormal signal areas in the cerebellum and left temporal lobe. These findings met the diagnostic criteria of serum-negative NMOSD. In this report we also evidenced a temporal relationship between onset of the symptoms and Vaxzevria, that makes it plausible a causal relationship. Support this hypothesis the increasing number of NMOSD recently described with other vaccines ([Jarius et al, 2016](#)) and the two instances of myelitis reported in clinical trials with Vaxzevria ([Voysey et al, 2021](#)). However, unlike these prior efforts, despite steroid therapy and plasmapheresis, patient's outcome remained poor. Although we cannot rule the exact mechanism underlying this phenomenon, we speculate that Vaxzevria may induce, in some cases, a widespread inflammatory reaction, probably mediated by the effect of some cytokines, such as tumor necrosis factor, interleukin 1-beta, and interleukine-17 that affects the clinical outcome ([Román et al; 2021](#)). In conclusion, although it is difficult, if not impossible, to establish a causal relationship between vaccination and CNS demyelinating disease through the temporal association of rare events described in case reports such as this, we nevertheless believe it is important to make such cases known, both to contribute to the continued development of safe methods of vaccination against SARS-CoV-2, as well as to provoke further investigation into the pathogenesis of NMOSD, which may lead to a more refined nosology of this evolving spectrum of disease.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.nerep.2021.100016](https://doi.org/10.1016/j.nerep.2021.100016).

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